

Bladder Cancer A Major Disease

Andrea B. Apolo, MD

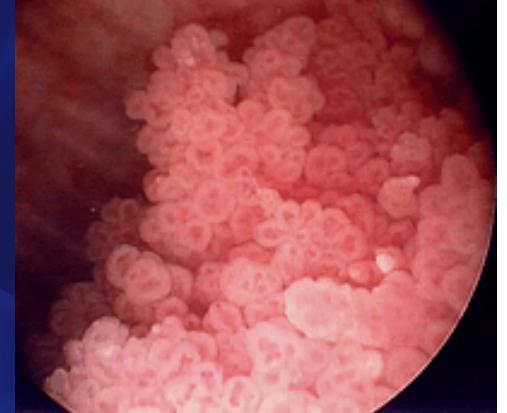
Chief, Bladder Cancer Section
Genitourinary Malignancies Branch

National Cancer Institute

National Institutes of Health

March 31, 2015

Urothelial Carcinoma



- In the US, 74,690 new cases and 15,580 deaths will occur in 2014
- 4th most common malignancy in men and the 9th most common in women
- Median age is 73 years
- 3:1 male to female ratio
- Is a chemosensitive disease but response durations are short
- No standard 2nd line therapy in the United States
- Median survival for metastatic disease is approximately 12–14 months
- We are in desperate need for effective therapies

FDA Approved Drugs for Genitourinary Tumors in the last Nine Years

Year of FDA approval			
2006			
2007			
2008			
2009			
2010			
2011			
2012			
2013			
2014			

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FDA Approved Drugs for Genitourinary Tumors in the last Nine Years

Year of FDA approval	Renal Cell Carcinoma		
2006	sunitinib		
2007	temsirolimus		
	sorafenib		
2008			
2009	everolimus		
	bevacizumab		
	pazopanib		
2010			
2011			
2012	axitinib		
2013			
2014			

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FDA Approved Drugs for Genitourinary Tumors in the last Nine Years

Year of FDA approval	Renal Cell Carcinoma	Prostate Cancer
2006	sunitinib	
2007	temsirolimus	
	sorafenib	
2008		degarelix
2009	everolimus	
	bevacizumab	
	pazopanib	
2010		sipuleucel-T
		cabazitaxel
2011		abiraterone
		denosumab
	axitinib	enzalutamide
2013		alpharadin
2014		

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		abiraterone	
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2014			

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	axitinib	enzalutamide	
		alpharadin	
2014			

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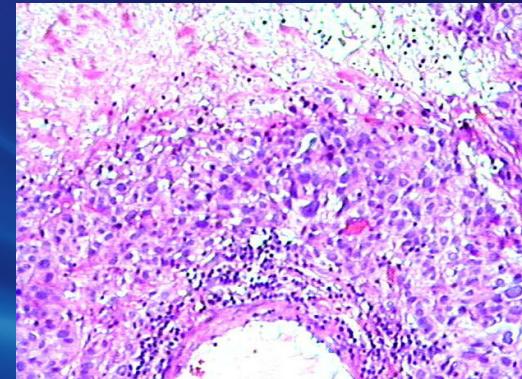
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Bladder Cancer Risk Factors

- Smoking: accounts 50% in US, 3-5 folds higher risk in smokers. (JAMA 2011)
- Aromatic amines, certain occupations: leather/rubber/painting (analine dyes, vinyl, etc)
- Prior pelvic irradiation
- Prior cyclophosphamide
- Schistosomiasis (squamous cell carcinoma and TCC)
- Chronic cystitis (squamous cell ca)
- HNPCC (with upper tract tumors)

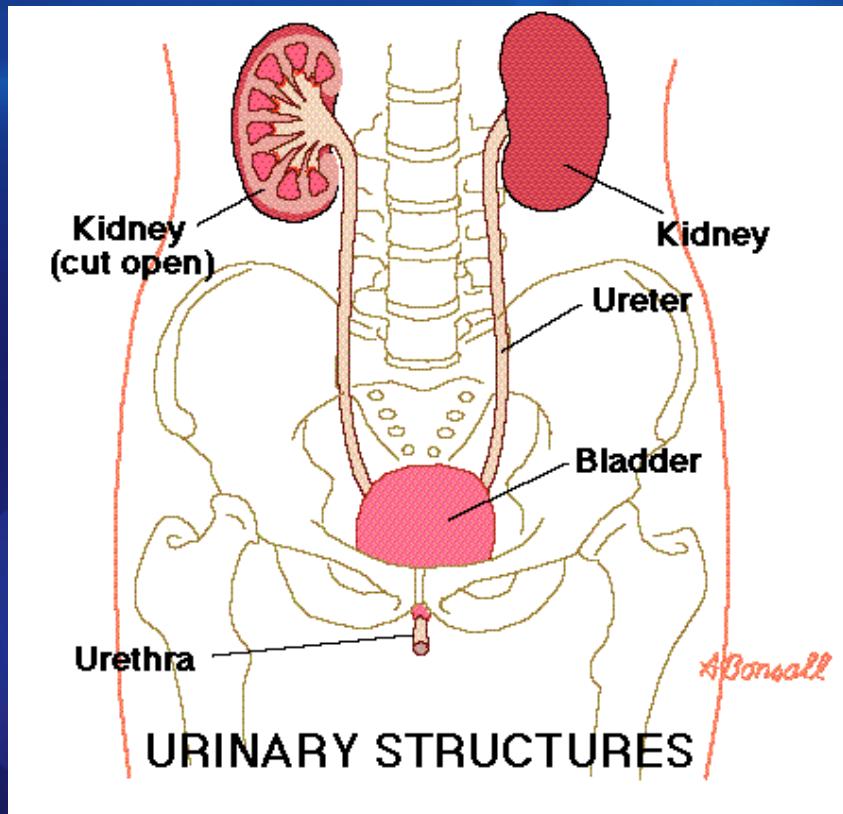


Histology



Transitional Cell Carcinoma	90%
Squamous Cell Carcinoma	5%
Adenocarcinoma	0.5-2%
Small Cell Carcinoma	<1%

Urothelial Carcinoma



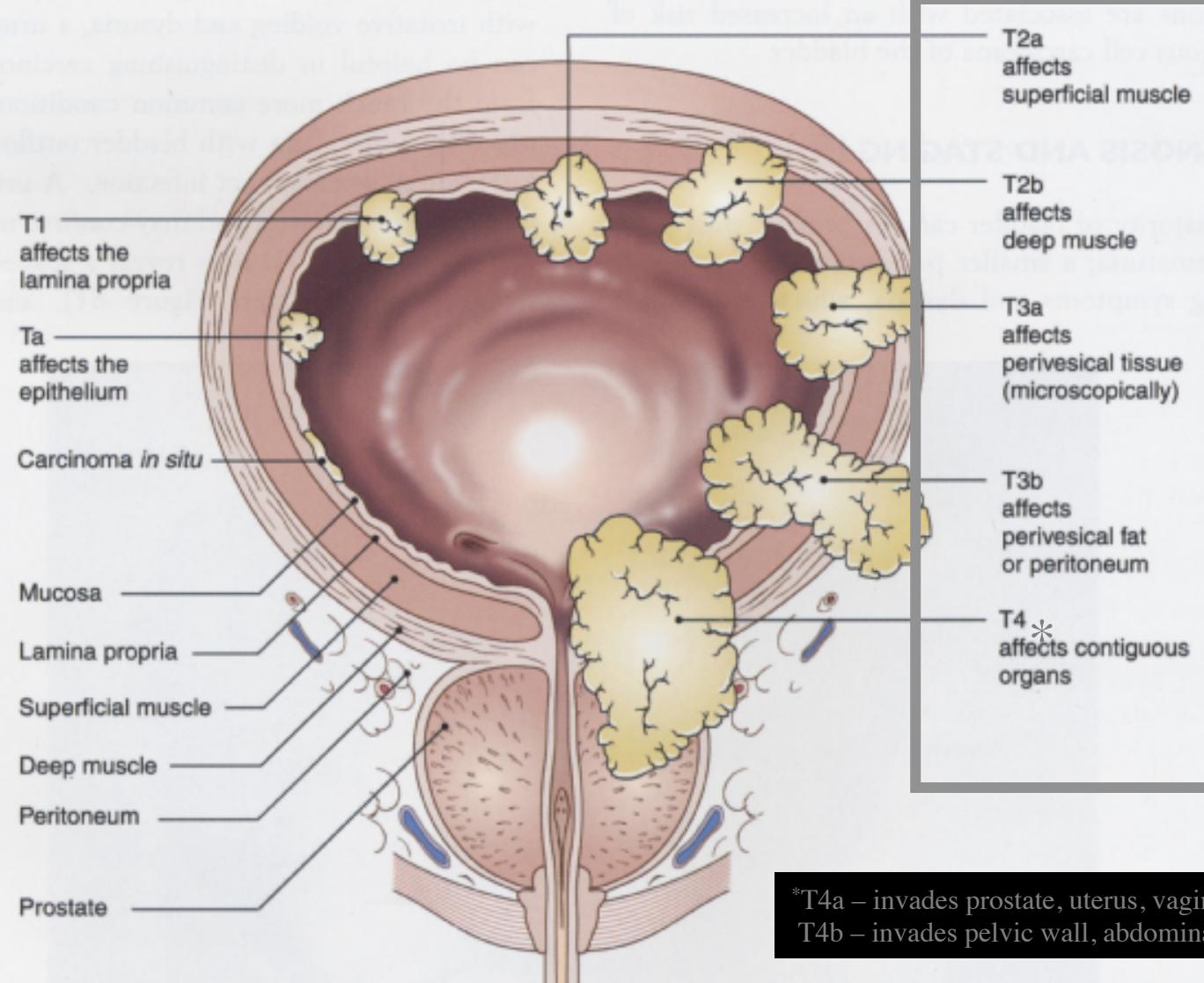
Transitional Cell Carcinoma

Includes:

- Bladder
- Ureter
- Renal pelvis (5-10% of all renal tumors)

Have a similar natural history and similar management principles may be applied to each.

Bladder Cancer Staging

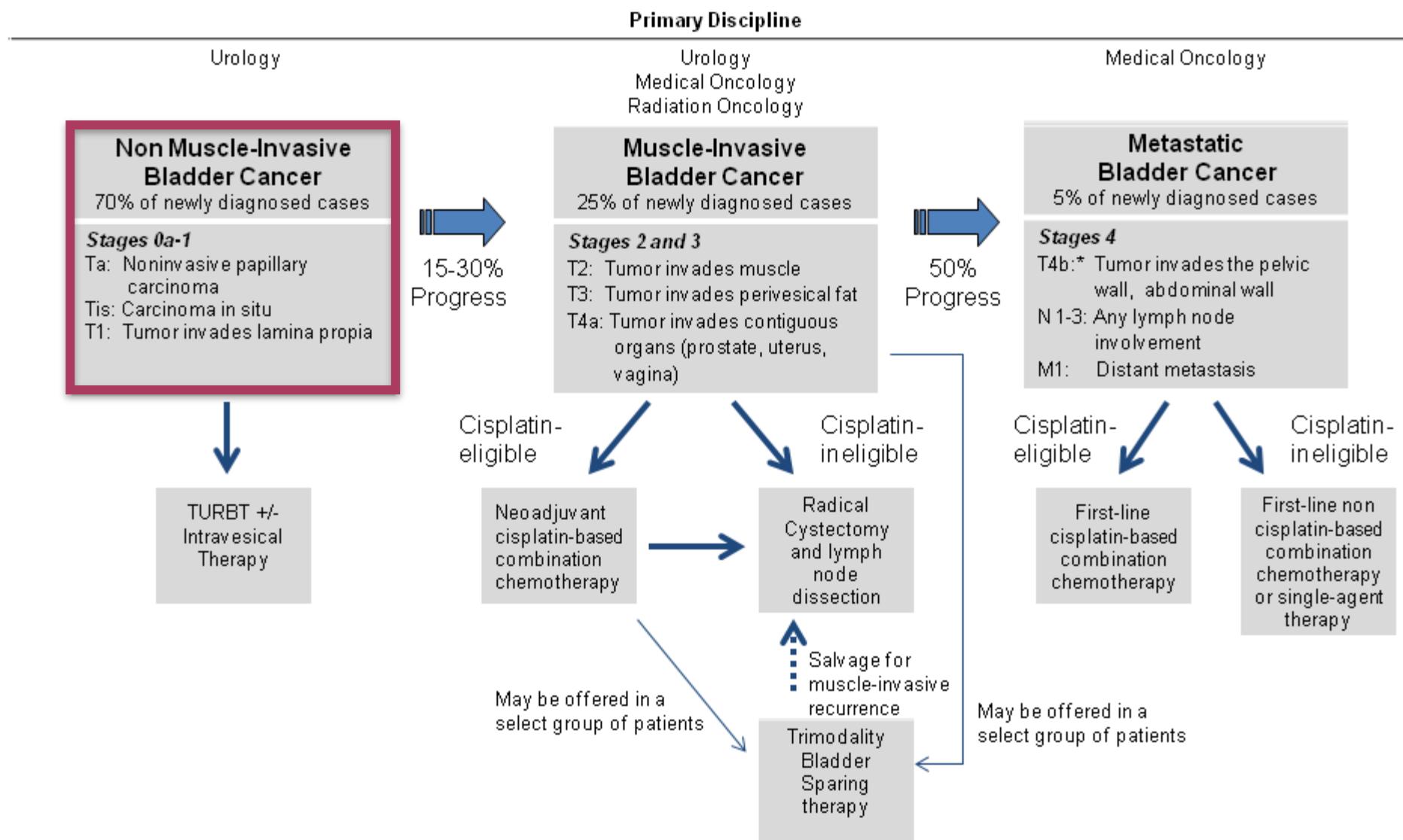


Bladder Cancer Clinical presentation



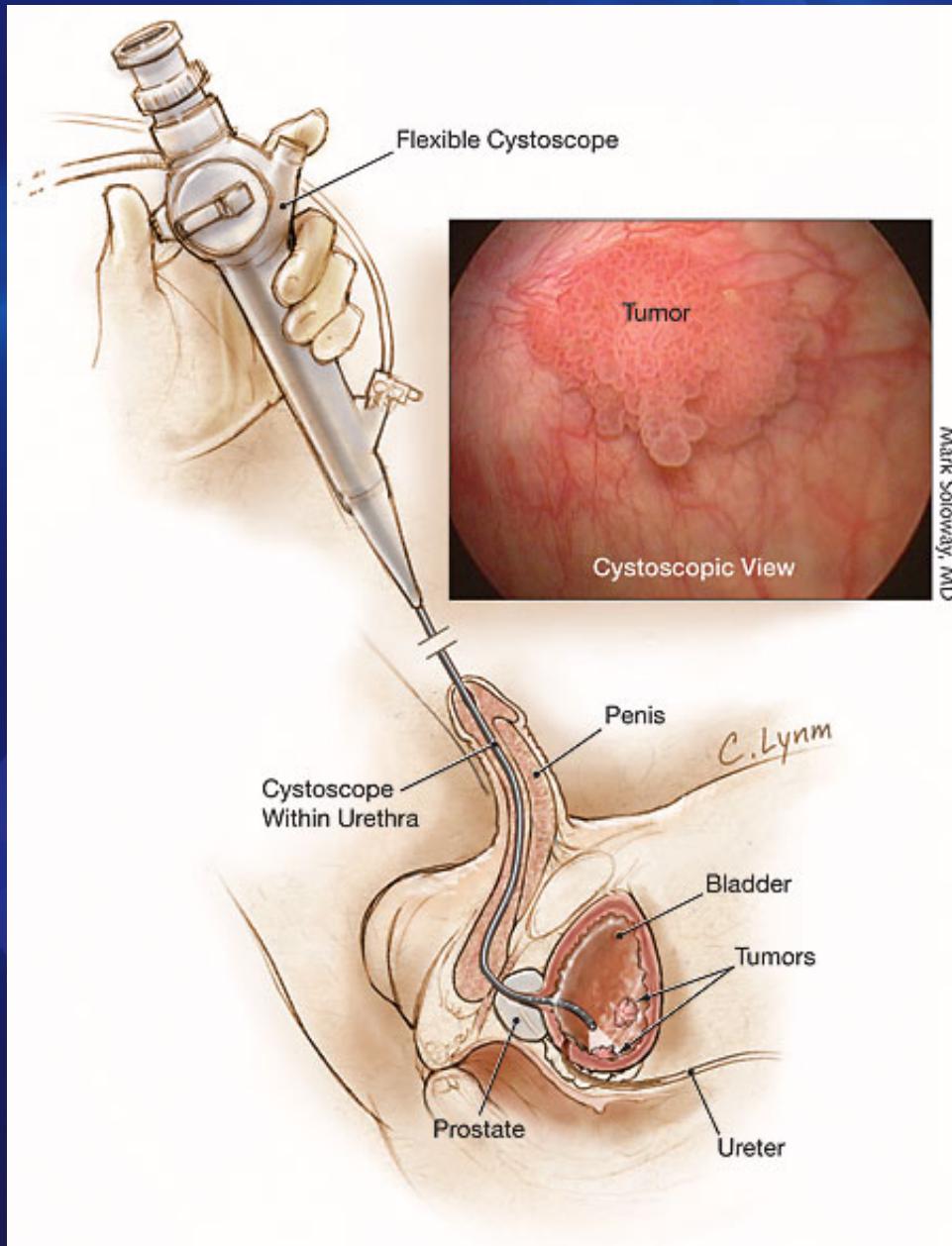
- Painless gross hematuria 80%
- Irritative symptoms 20%: urinary frequency, urgency and dysuria, suggesting Cis and muscle invasive dx.
- Some asymptomatic: microscopic hematuria.
- Advanced dx: urinary obstruction or involved organ symptoms.

Bladder Cancer Management by Stage

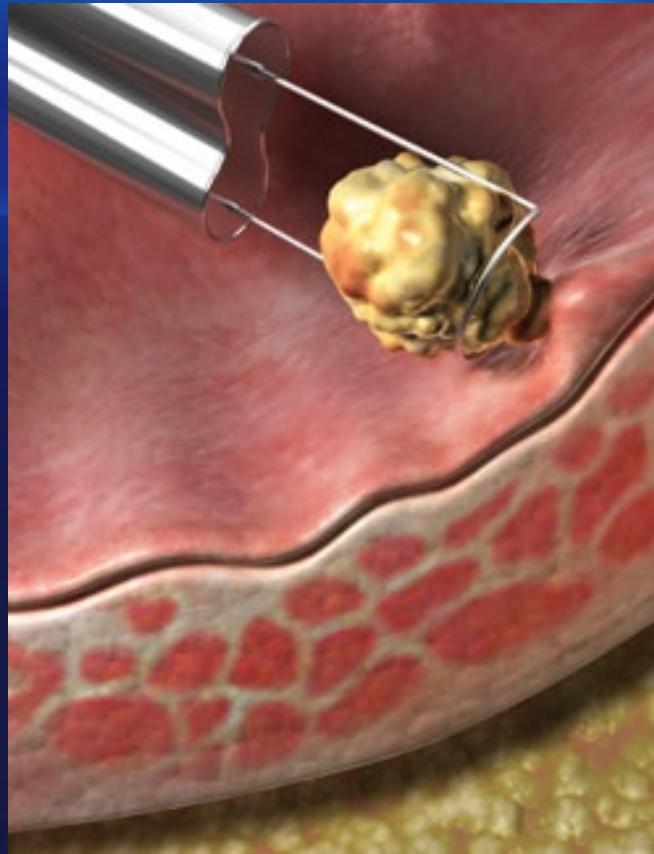


Cystoscopic Evaluation

Transurethral resection (TUR) of the bladder is a surgical procedure that is used both to diagnose bladder cancer and to remove cancerous tissue from the bladder



Transurethral Resection of Bladder Tumor



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Primary Non-Muscle Invasive Bladder Cancer Risk Groups

Stratified by Tumor Grade and Stage

Low Risk

- Grade I, stage Ta disease
- Single grade I, stage T1 tumor

Recurrence 37%, progression 0%, mortality 0%

Intermediate Risk

- Multiple grade I, stage T1 tumors
- Grade II, stage Ta disease
- Single grade II, stage T1 tumor

Recurrence 45%, progression 1.8%, mortality 0.73%

High Risk

- Multiple grade II, stage T1 tumors
- Grade III, stage Ta or T1 disease
- Carcinoma in situ

Recurrence 54%, progression 15%, mortality 9.5%

Millan-Rodriguez F, et al. *J Urol.* 2000;164:680.

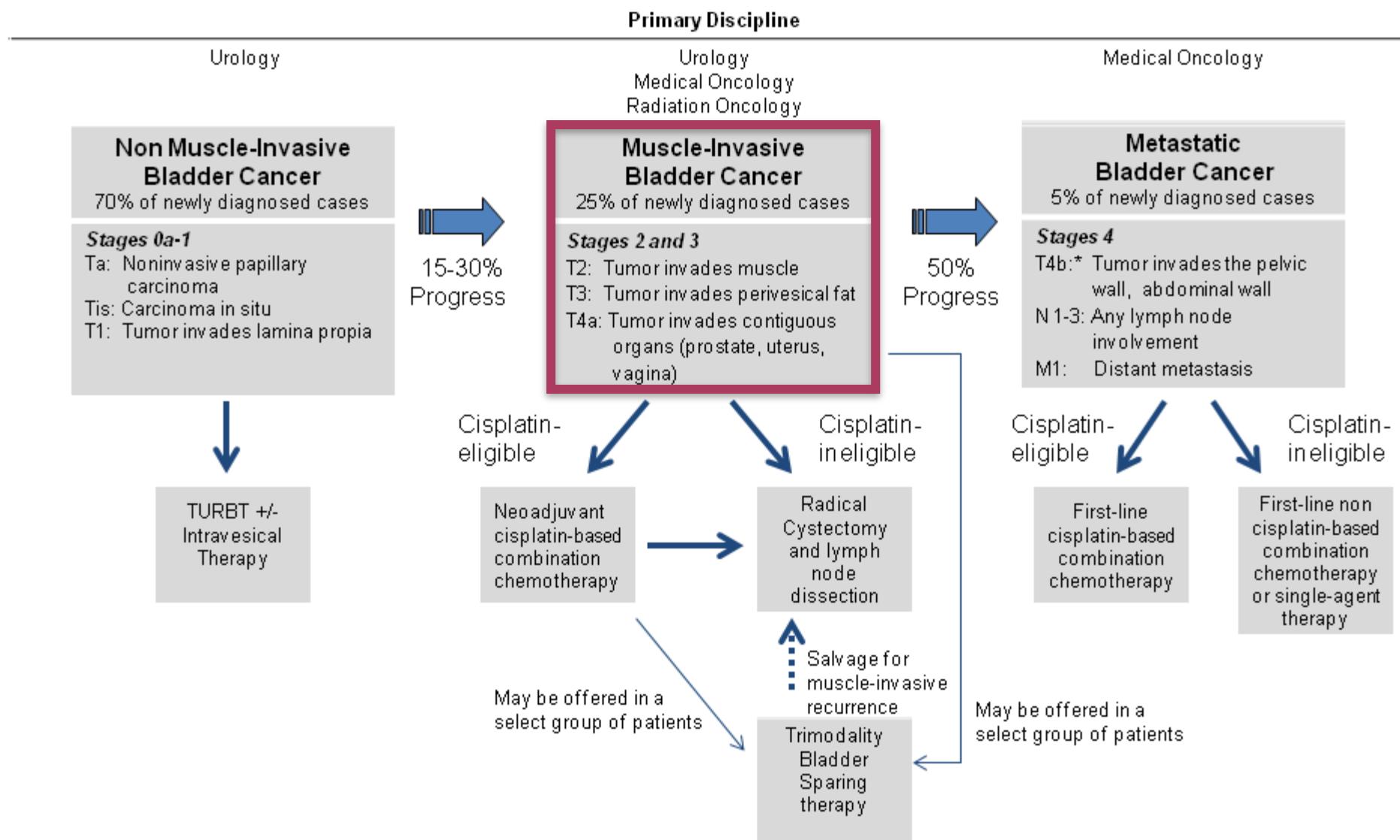
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Intravesical Therapy

Indications

- Multiple tumor recurrences or rapidly recurrent disease
- Large (>5 cm) solid bladder tumor
- Lamina propria invasion
- Multifocal disease
- High-grade Ta disease or any grade T1 disease
- Carcinoma in situ
- Extravesical involvement (prostatic urethra)
- Postresection positive cytology (after negative workup of upper urinary tracts)

Bladder Cancer Management by Stage



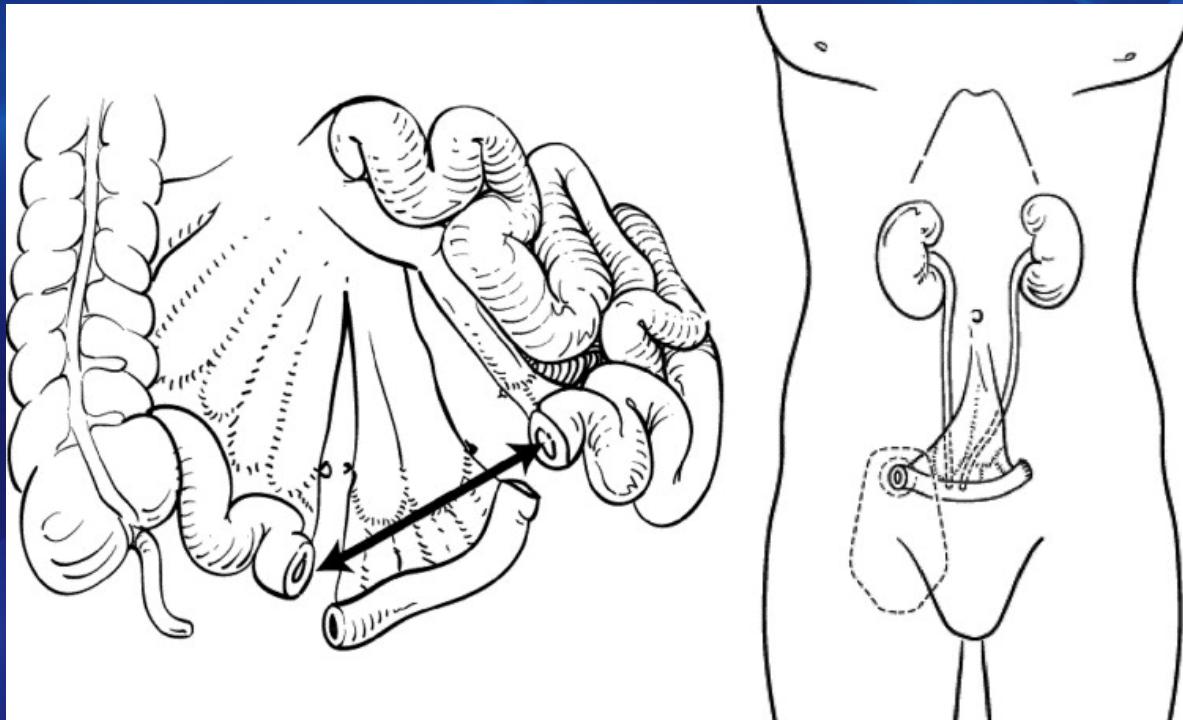
Muscle Invasive Disease

- Radical cystectomy (includes bladder, regional pelvic LNs, distal ureters)
 - in men, prostate gland, seminal vesicles, and proximal urethra are included
 - in women, the urethra, uterus, fallopian tubes, anterior vaginal wall and surrounding fascia are included

Urinary Diversion

- Ileal conduit
- Continent cutaneous reservoir
- Orthotopic urethral diversions (neobladder)

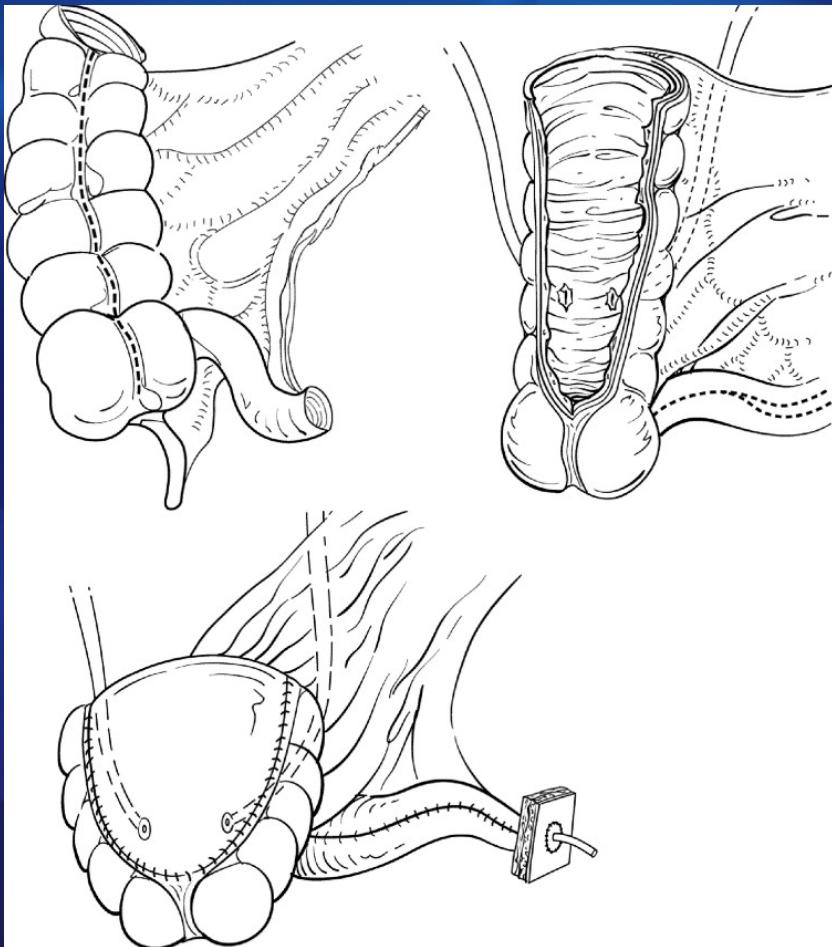
Ileal conduit



An isolated segment of the ileum is exteriorized in the form of a stoma through the abdominal wall with an appliance secured for continuous drain of urine.

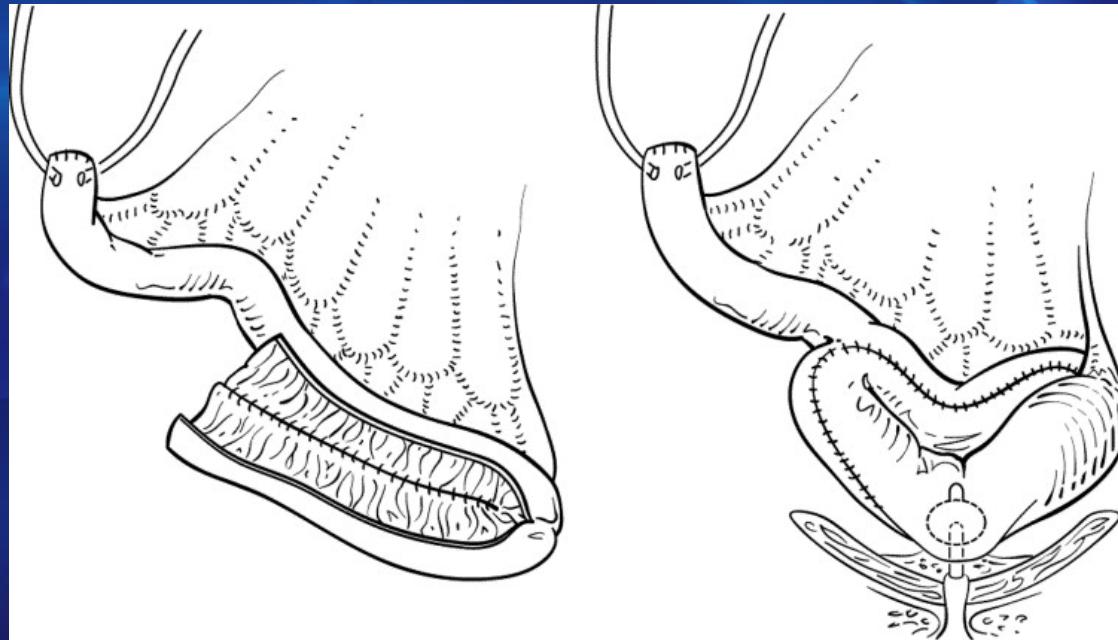
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Continent cutaneous reservoirs



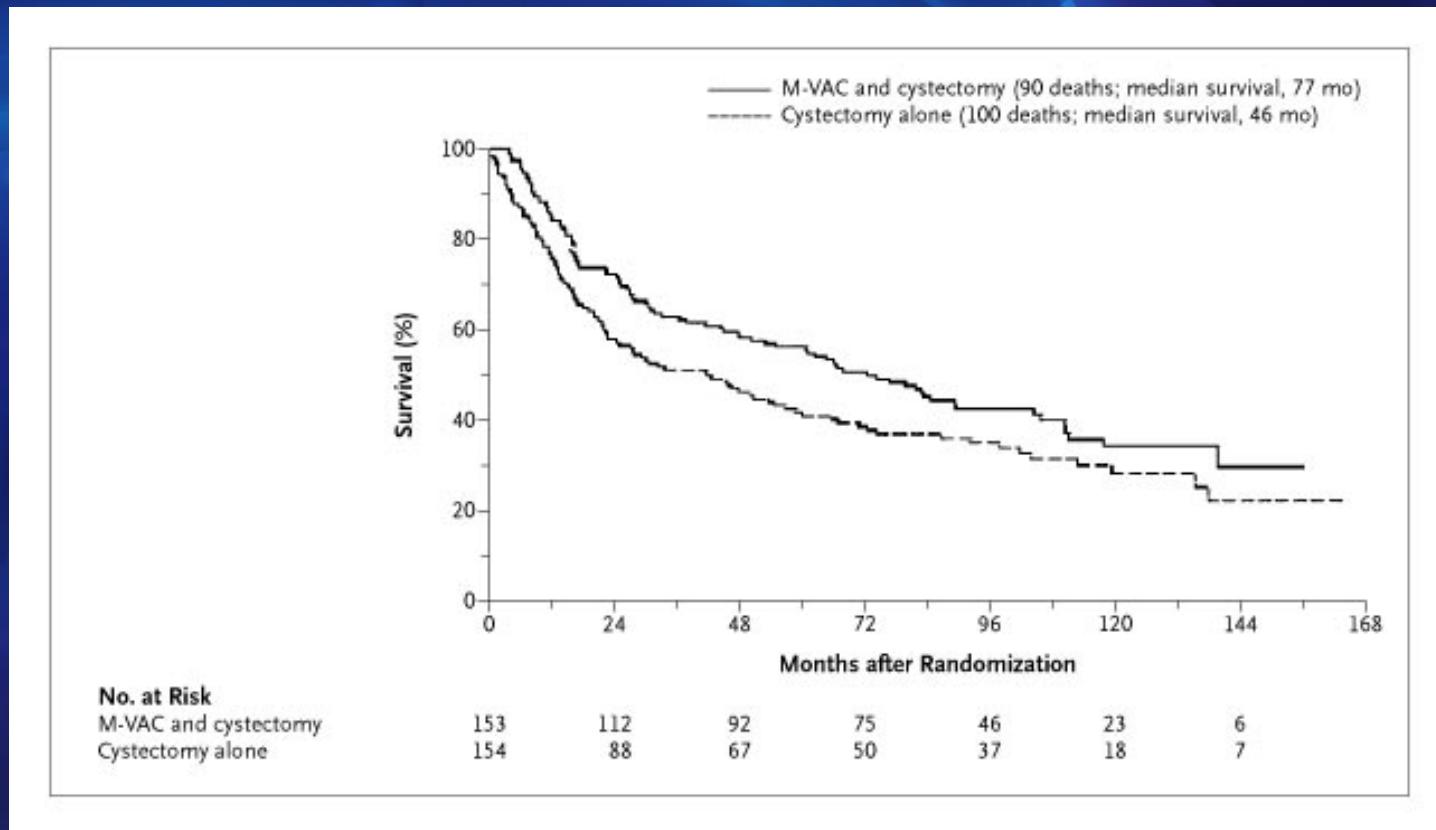
- A pouch is made of detubularized bowel for urinary storage
- A tapered bowel segments connects to skin
- Requires intermittent clean self catheterization

Orthotopic urethral diversions (neobladder)



- Spherical pouch is made from detubularized bowel for urinary storage
- Ureters are anastomized to the pouch which is then anastomized to native urethra

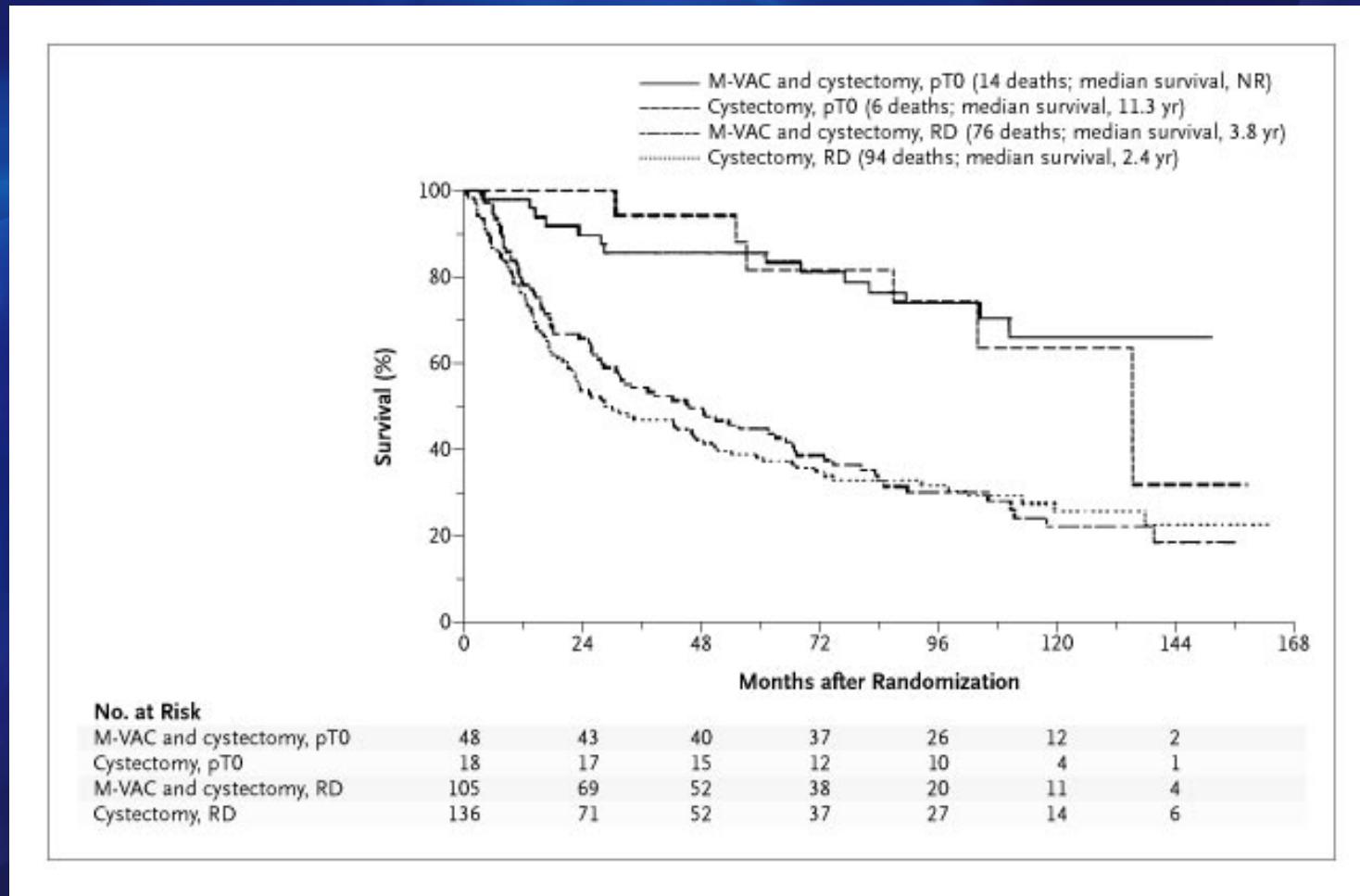
Survival among Patients Randomly Assigned to Receive Methotrexate, Vinblastine, Doxorubicin, and Cisplatin (M-VAC) Followed by Cystectomy or Cystectomy Alone, According to an Intention-to-Treat Analysis



Grossman, H. B. et. al. N Engl J Med 2003;349:859-866

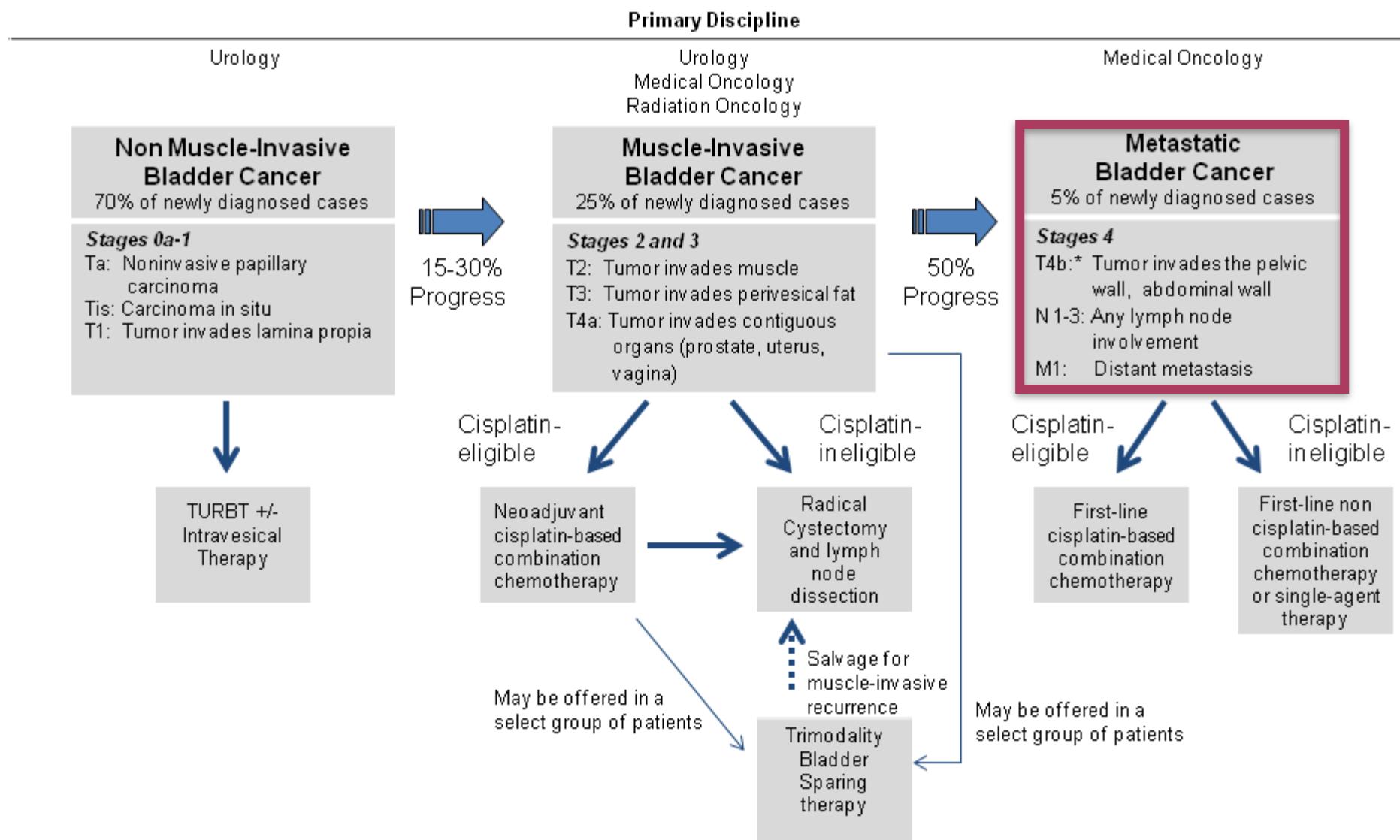
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Survival According to Treatment Group and Whether Patients Were Pathologically Free of Cancer (pT0) or Had Residual Disease (RD) at the Time of Cystectomy



Grossman, H. B. et. al. N Engl J Med 2003;349:859-866

Bladder Cancer Management by Stage



MVAC Randomized Trials

Investigators	Trial	No. Pts.	Response Rate	Median Survival
Loehrer et al (ECOG) JCO 10:1066, 1992	MVAC	120	39% ($p = .0001$)	12.5 mos ($p = .0002$)
	Cisplatin	126	12%	8.2 mos
.....				
Logothetis et al (MDA) JCO 8:1050, 1990	MVAC	55	65% ($p < .05$)	11.2 mos ($p = .003$)
	CisCA	55	46%	8.3 mos

Randomized Phase III Study In Metastatic Bladder Cancer

GC

- Gemzar 1000 mg/m² day 1, 8 and 15
- Cisplatin 70 mg/m² day 2

MVAC

- Methotrexate 30 mg/m² day 1, 15 and 22
- Vinblastine 3 mg/m² day 2, 15 and 22
- Adriamycin 30 mg/m² day 2
- Cisplatin 70 mg/m² day 2

GC versus MVAC Survival Analysis

	G-C	MVAC
Overall Survival	13.8 months	14.8 months
Response Rate	49.4%	45.7%
CR	12.2%	11.9%
PR	37.2%	33.8%
SD	33.5%	32.5%
Median TTP	7.4 months	7.4 months
Median TTF	5.8 months	4.6 months

GC versus MVAC

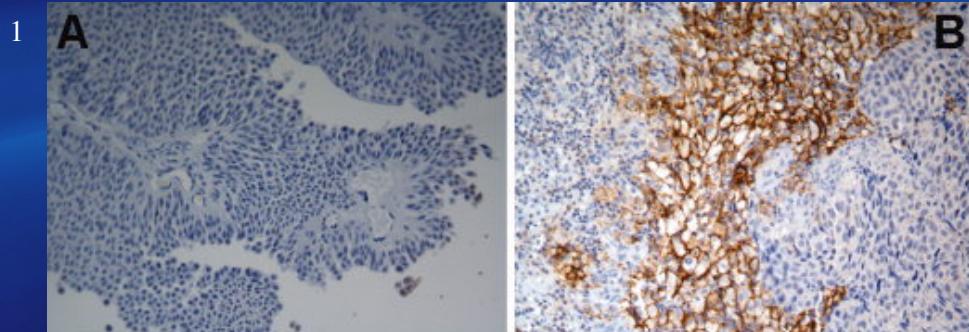
Most important toxicity differences

Toxicity	GC	MVAC
Neutropenic fever	2%	14%
Neutropenic sepsis	1%	12%
Mucositis (grade 3/4)	1%	22%
Toxic deaths	1%	3%

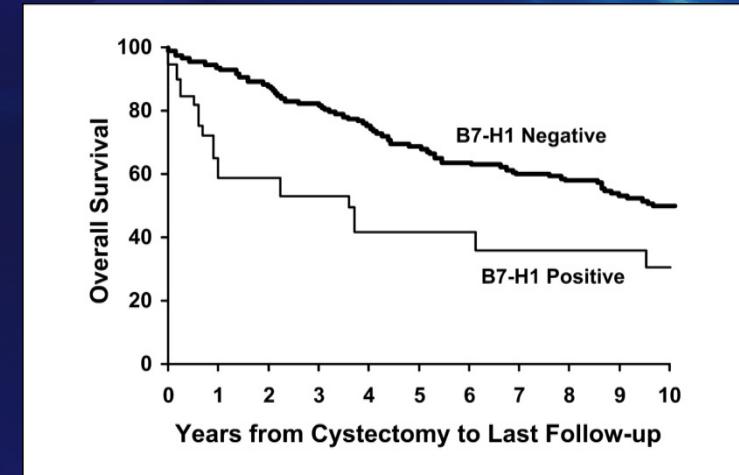
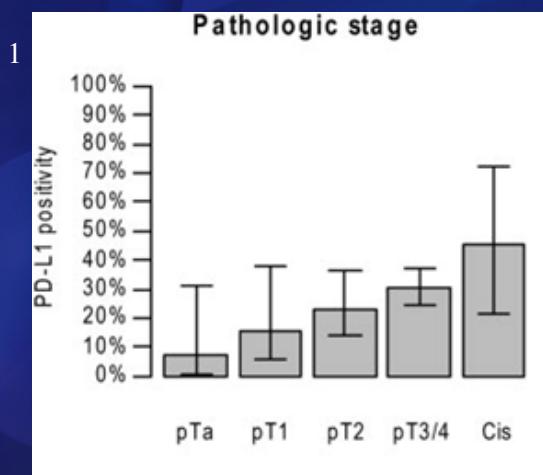
What Is New in Systemic Therapy for Urothelial Tumors?

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We are in the beginning of an immunotherapy revolution in oncology



- Immune check point therapy has demonstrated significant clinical activity in multiple solid tumors
- PD-L1 is highly expressed in urothelial cancer of the bladder



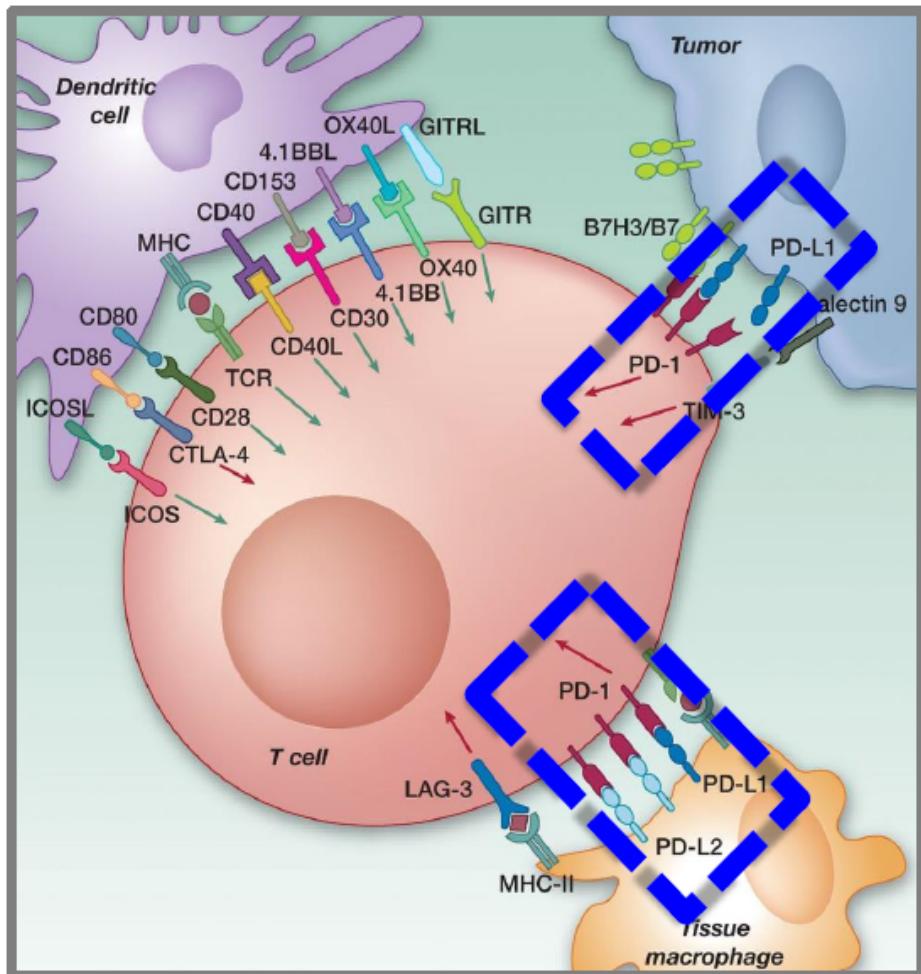
1. Inman BA, Sebo TJ, Frigola X, et al Cancer. 2007 15;109(8):1499-505
2. Boorjian S A et al. Clin Cancer Res 2008;14:4800-4808

3. Xylinas E et al. Eur J Surg Oncol. 2014 Jan;40(1):121-7
4. Nakanishi J et al. Cancer Immunol Immunother 2007 56(8):1173-82

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PD-1 Pathway and Immune Surveillance



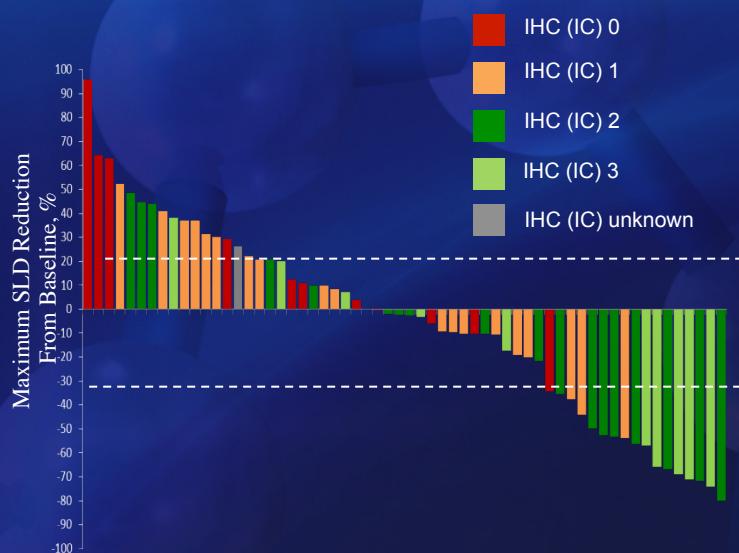
- PD-1 is a negative co-stimulatory receptor expressed primarily on activated T cells
- Binding of PD-1 to its ligands PD-L1 and PD-L2 inhibits effector T-cell function
- Expression of PD-L1 on tumor cells and macrophages can suppress immune surveillance and permit neoplastic growth

Melero I et al. *Clin Cancer Res.* 2013;19:997-1008. Plimack E, et al. *ESMO LBA23 Ann Oncol.* 2014;25:1-41

Keir ME et al. *Annu Rev Immunol.* 2008;26:677-704; Pardoll DM. *Nat Rev Cancer.* 2012;12:252-64; Hirano F et al. *Cancer Res.* 2005;65:1089-96.

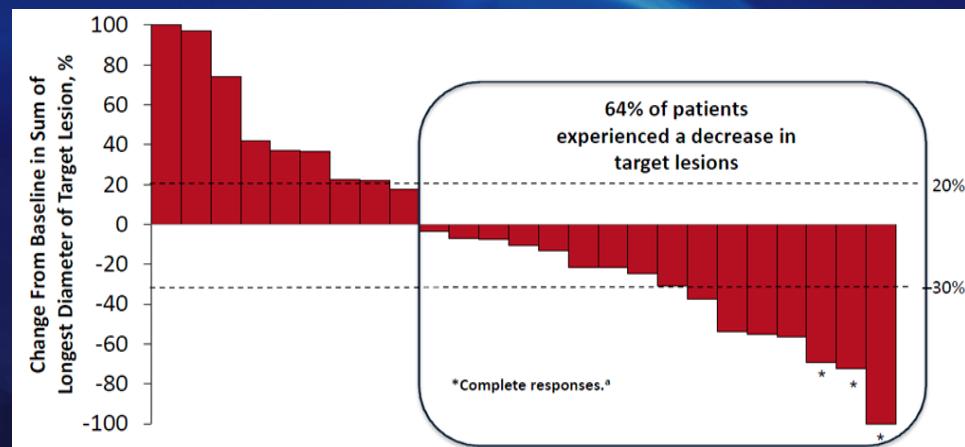
Checkpoint Inhibition in Urothelial Carcinoma

MPDL3280A Summary of ORR



Powles T, et al., Nature. 2014;515:558-562.

Pembrolizumab Summary of ORR

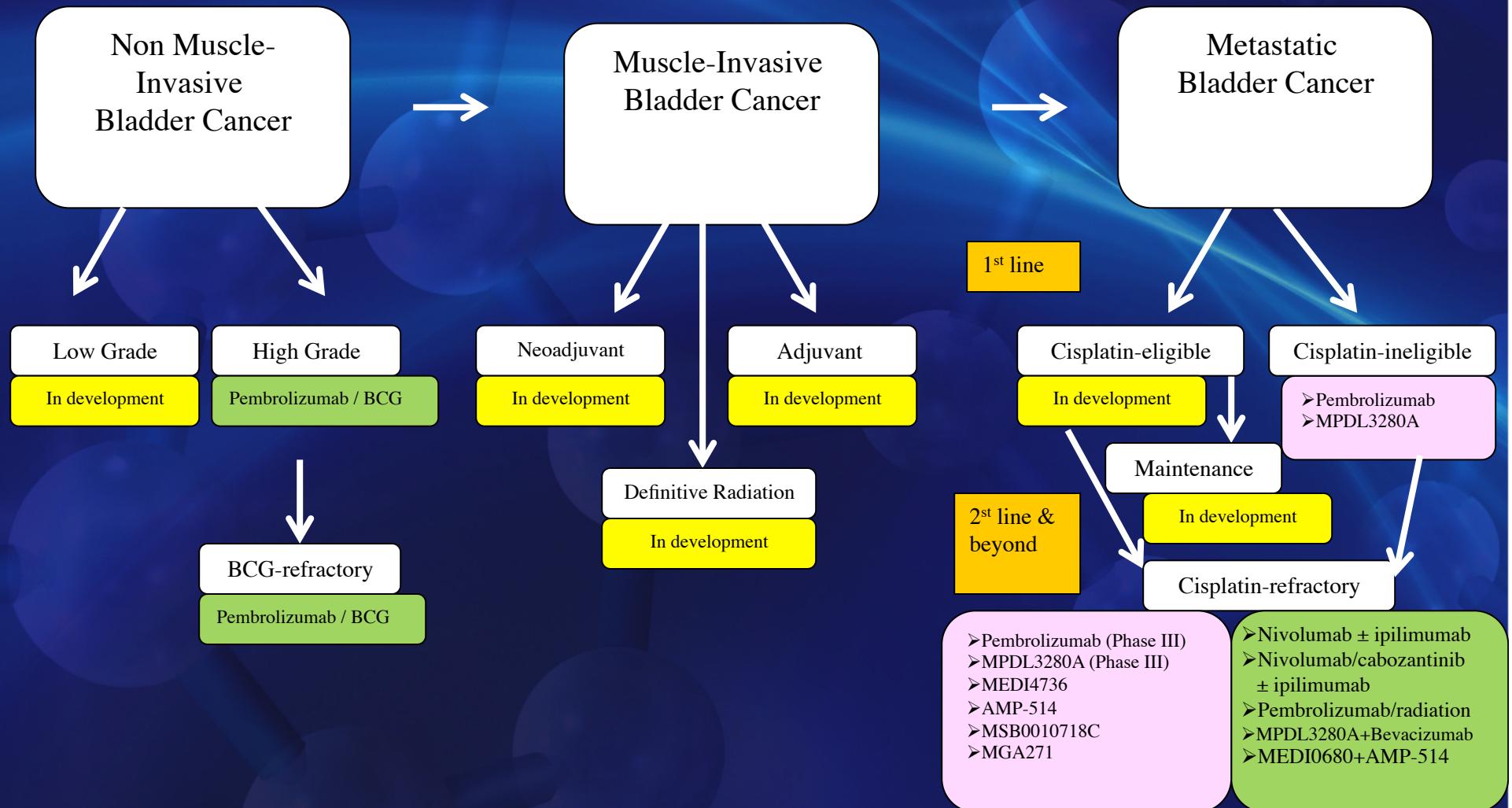


Plimack E, et al. ESMO LBA23 Ann Oncol. 2014;25:1-41

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Checkpoint Clinical trials in Bladder Cancer



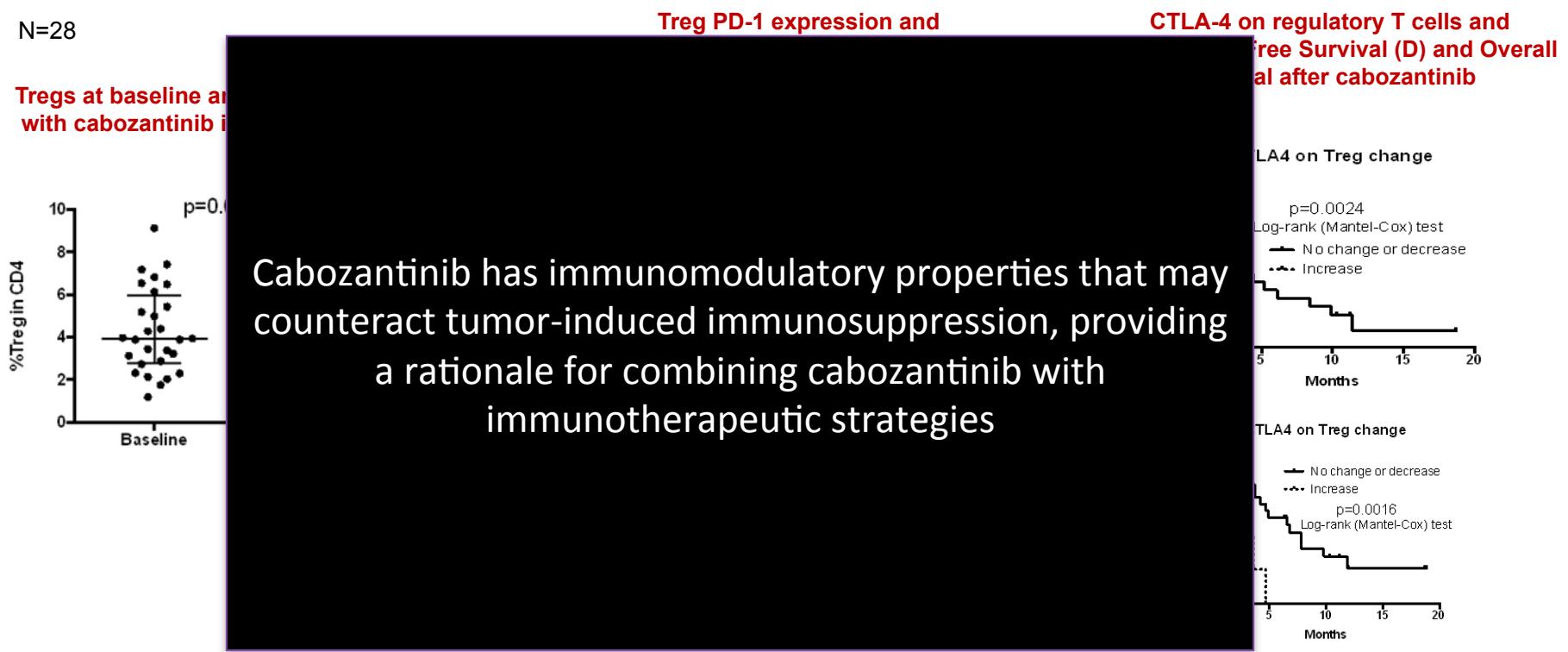
Agents that can enhance the immune response

- Immunotherapies
 - Vaccines
 - CTLA-4 inhibitors
 - Adoptive cell transfer
- Radiation
- Chemotherapy
- Tyrosine kinase inhibitors

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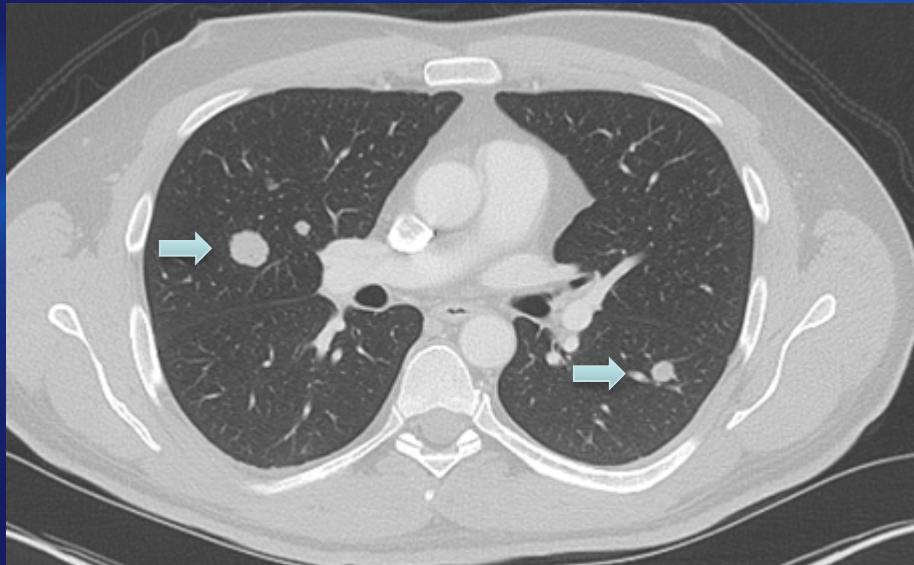
Changes in immune infiltrating cells in bladder cancer patients treated with cabozantinib



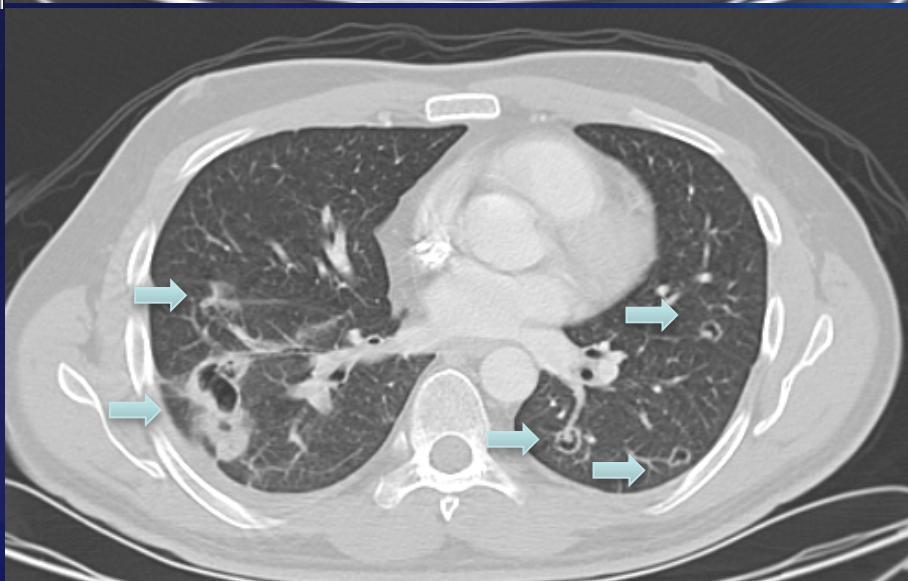
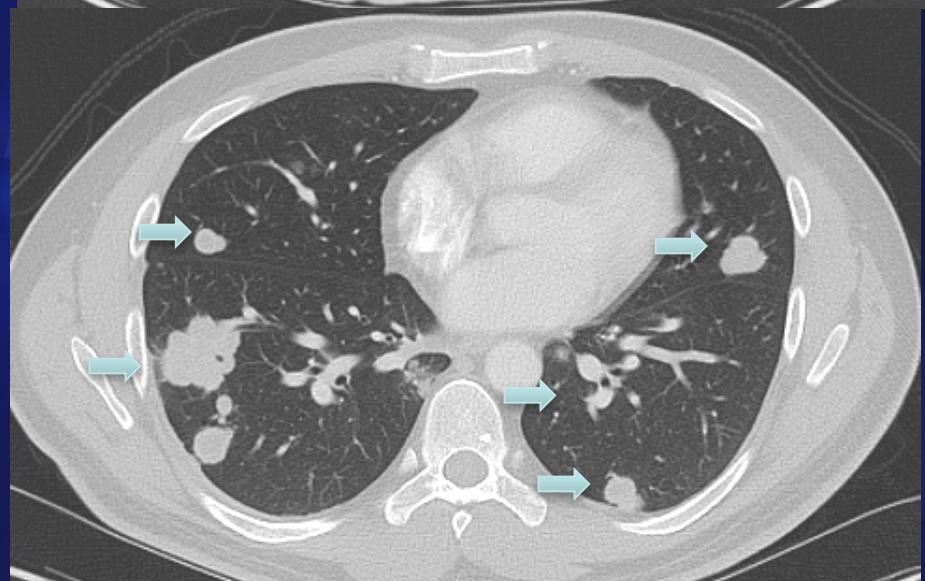
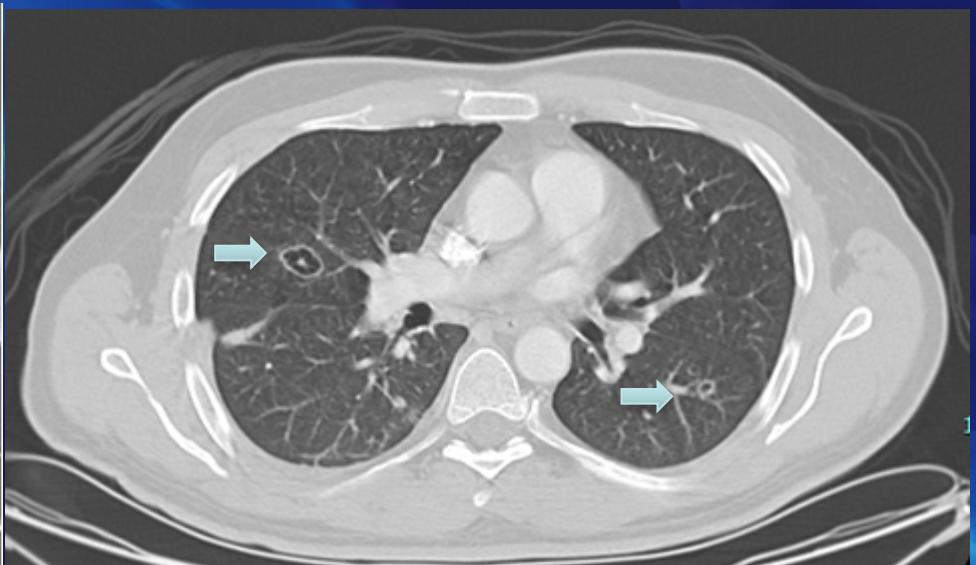
- Treatment with cabozantinib lead to:
- Decrease Tregs among CD4+ T-cells, increase PD-1 expression in Tregs, decrease CTLA-4 expression on Tregs.

Chest CT scan of a metastatic urothelial cancer patient on single agent Cabozantinib

Baseline

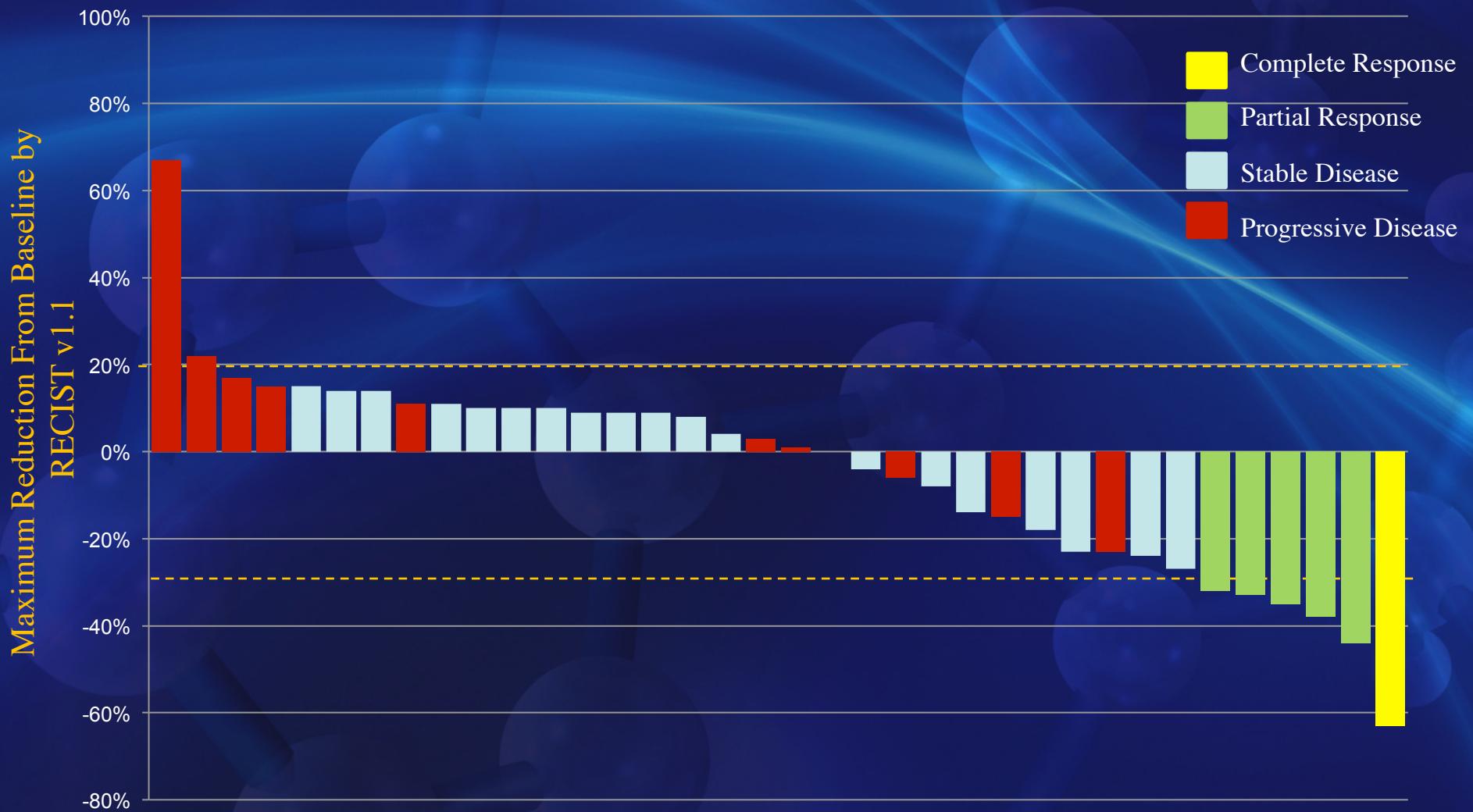


Post-cabozantinib



te

Cabozantinib: Preliminary Summary of ORR in bladder cancer patients



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Combination Therapy may be the answer

- Potentially increasing T cell infiltration into tumors and “priming the tumor” for a better response to checkpoint inhibition
- Caution of increase toxicity with combinations

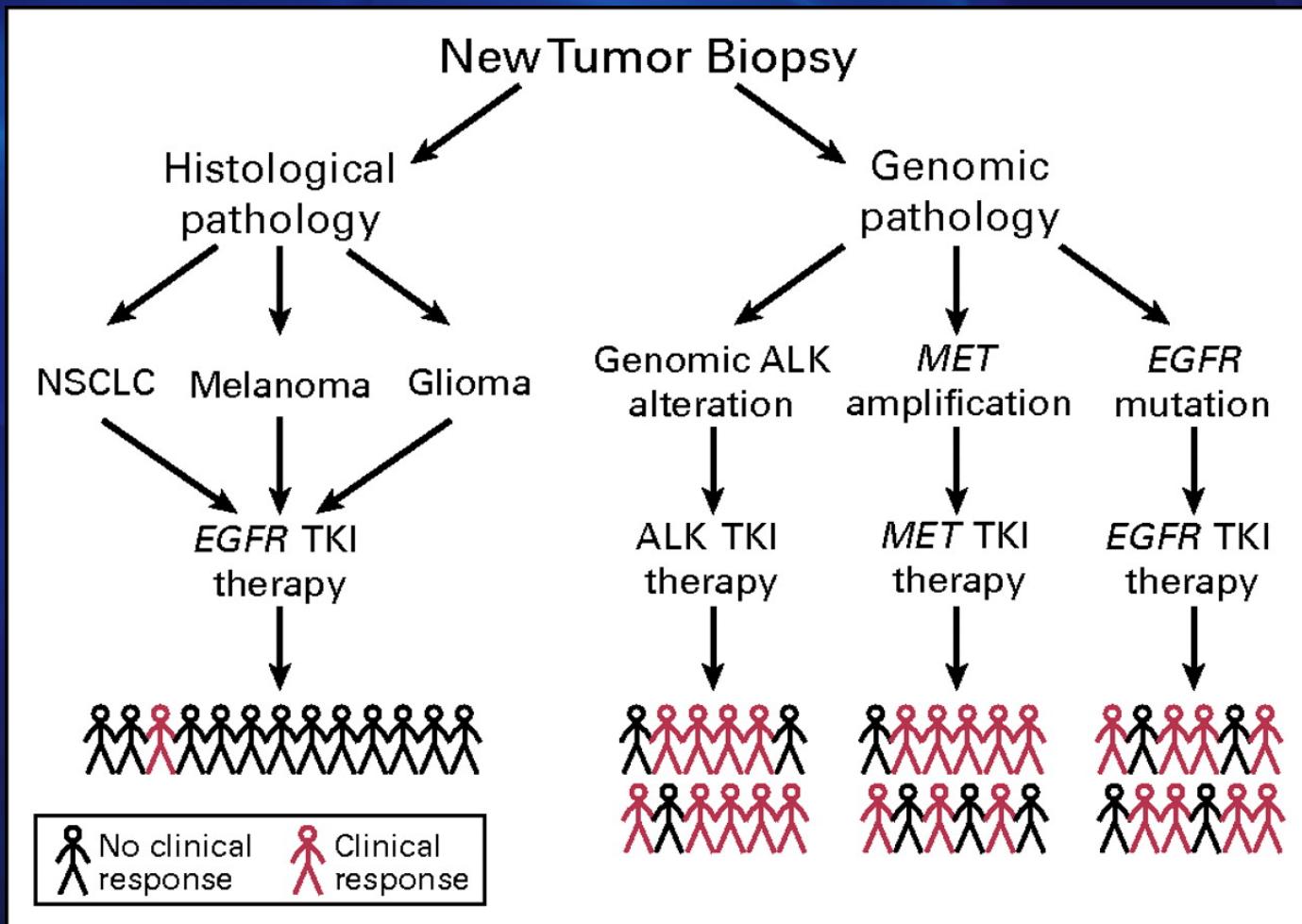
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Second-Line Single Agent Targeted Therapies Reported in Metastatic Urothelial Cancer

Author	Year	Agent	Target	Study type	n	OS (months)	RR%
Gomez-Abuin	2007	Bortezomib	Proteasome inhibitor	Phase II	20	NR	0
Rosenberg	2008	Bortezomib	Proteasome inhibitor	Phase II	25	5.7	0
Wulffing	2009	Lapatinib	HER1 and HER2	Phase II	59	4.5	3
Petrylak	2009	Gefitinib	EGFR	Phase II	31	3	3
Dreicer	2009	Sorafenib	B-Raf,c-Raf, VEGFR-2/3, PDGFR-b	Phase II	27	6.8	0
Gallagher	2010	Sunitinib	VEGFR-1/2, C-KIT, PDGFR a/b,FLT3 and RET	Phase II	45	6.9	7
Twardowski	2010	Aflibercept	VEGF, PDGF	Phase II	22	NR	4.5
Cheung	2010	Vorinostat	SAHA: histone deacetylase	Phase II	14	4.3	0
Stadler	2011	Volasertib	Polo-like kinase 1	Phase II	31	NR	19
Milowsky	2011	Everolimus	PI3K/Akt/mTOR	Phase II	45	10.5	5
Pili	2011	Pazopanib	VEGFR1/2/3, PDGFR a/b,c- Kit	Phase II	19	NR	0
Necchi	2012	Pazopanib	VEGFR1/2/3, PDGFR a/b,c- Kit	Phase II	41	4.7	17
Lerner	2012	Tamoxifen	ER-B	Phase II	28	NR	NR
Milowsky	2013	Dovitinib	FGFR3	Phase II	44	NR	0

Precision Cancer Therapy With Selective Kinase Inhibitors



McDermott, U. et al. J Clin Oncol; 27:5650-5659 2009

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TCGA's Significantly Mutated Genes

Gene	TCGA (%)
TP53	49
KMT2D	27
ARID1A	25
KDM6A	24
PIK3CA	20
EP300	15
CDKN1A	14
RB1	13
ERCC2	12
STAG2	11
ERBB3	11
FBXW7	10
RXRA	9

- **69% of tumors harbored potential therapeutic targets**

- **76% of the tumors had an inactivating mutation in chromatin regulatory genes**
 - These epigenetic alterations also suggest new possibilities for bladder cancer treatment

Gene	TCGA (%)
FGFR3	12
ELF3	8
NFE2L2	8
TSC1	8
KLF5	8
TXNIP	7
FOXQ1	5
CDKN2A	5
RHOB	5
PAIP1	5
FOXA1	5
BTG2	5
HRAS	5
ZFP36L1	5
RHOA	4
CCND3	4

TCGA's Significantly Mutated Genes and Potential Targeted Agents

Gene	TCGA (%)	Potential Agent	Target	
TP53	49	ALT- 801	p53	
KMT2D	27			
ARID1A	25			
KDM6A	24			
PIK3CA	20	everolimus	mTOR	
		everolimus	mTOR	
		sirolimus	mTOR	
		sirolimus	mTOR	
		AZD5363	PI3K	
		AZD8835	PI3K	
		BGJ398/ BYL719	FGFR 1/2/3, PI3K	
		buparlisib (BKM120)	PI3K	
		MLN1117	PI3K	
		MEK162 plus BYL719	MEK1/2 and PI3K	
		nilotinib, everolimus, sorafenib, lapatinib, or pazopanib	multiple	
EP300	15	Mocetinostat	HDAC	
CDKN1A	14			
RB1	13			
ERCC2	12			
STAG2	11			
ERBB3	11	MM-141	ERBB3, IGF-1R	
FBXW7	10			
RXRA	9			

Gene	TCGA (%)	Potential Agent	Target	
FGFR3	12	Dovitinib	FGFR3	
		BGJ398	FGFR 1/2/3	
		BAY1163877	FGFR	
		BGJ398/ BYL719	FGFR 1/2/3, PI3K	
		CH5183284	FGFR 1/2/3	
		FPA144	FGFR2	
		GSK3052230	FGFR1	
		BIBF 1120	VEGFR, FGFR & PDGFR	
		ELF3	8	
		NFE2L2	8	
		TSC1	8	
		Everolimus	mTOR	
		Everolimus	mTOR	
		Everolimus	mTOR	
		Sirolimus	mTOR	
		Sirolimus	mTOR	
		KLF5	8	
		TXNIP	7	
		FOXQ1	5	
		CDKN2A	5	LEE011 CDK4/6, cyclin D 1/3, p16
		RHOB	5	
		PAIP1	5	
		FOXA1	5	
		BTG2	5	
		HRAS	5	
		ZFP36L1	5	
		RHOA	4	
		CCND3	4	LEE011 CDK4/6, cyclin D 1/3, p16

**TCGA's Significantly Mutated Genes and Potential Targeted Agents
in Muscle-Invasive or Metastatic Urothelial Carcinoma Currently under Investigation in Clinical Trials**

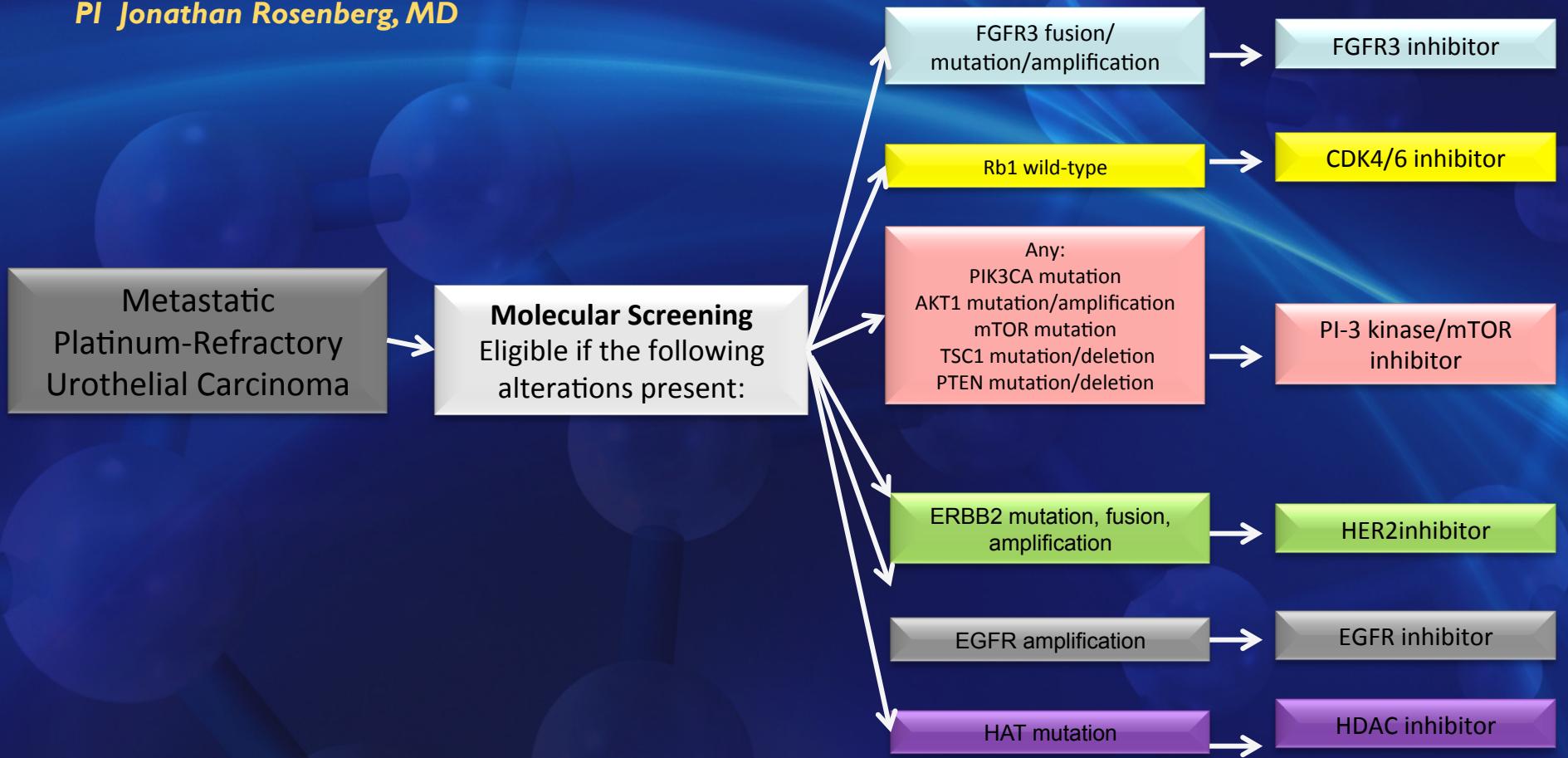
Gene	TCGA (%)	Potential Agent	Target	Clinical Trial
TP53	49	ALT- 801	p53	NCT01326871
KMT2D	27			
ARID1A	25			
KDM6A	24			
PIK3CA	20	everolimus	mTOR	NCT01182168
		everolimus	mTOR	NCT01215136
		sirolimus	mTOR	NCT01938573
		sirolimus	mTOR	NCT01522820
		AZD5363	PI3K	NCT01226316
		AZD8835	PI3K	NCT02260661
		BGJ398/ BYL719	FGFR 1/2/3, PI3K	NCT01928459
		buparlisib (BKM120)	PI3K	NCT01971489
		MLN1117	PI3K	NCT01449370
		MEK162 plus BYL719	MEK1/2 and PI3K	NCT01449058
		nilotinib, everolimus, sorafenib, lapatinib, or pazopanib	multiple	NCT02029001
EP300	15	Mocetinostat	HDAC	NCT02236195
CDKN1A	14			
RB1	13			
ERCC2	12			
STAG2	11			
ERBB3	11	MM-141	ERBB3, IGF-1R	NCT01733004
FBXW7	10			
RXRA	9			

Gene	TCGA (%)	Potential Agent	Target	Clinical Trial
FGFR3	12	Dovitinib	FGFR3	NCT01831726
		BGJ398	FGFR 1/2/3	NCT01004224
		BAY1163877	FGFR	NCT01976741
		BGJ398/ BYL719	FGFR 1/2/3, PI3K	NCT01928459
		CH5183284	FGFR 1/2/3	NCT01948297
		FPA144	FGFR2	NCT02318329
		GSK3052230	FGFR1	NCT01868022
		BIBF 1120	VEGFR, FGFR & PDGFR	NCT01349296
ELF3	8			
NFE2L2	8			
TSC1	8	Everolimus	mTOR	NCT02201212
		Everolimus	mTOR	NCT01182168
		Everolimus	mTOR	NCT01215136
		Sirolimus	mTOR	NCT01938573
		Sirolimus	mTOR	NCT01522820
KLF5	8			
TXNIP	7			
FOXQ1	5			
CDKN2A	5	LEE011	CDK4/6, cyclin D 1/3, p16	NCT0218773
RHOB	5			
PAIP1	5			
FOXA1	5			
BTG2	5			
HRAS	5			
ZFP36L1	5			
RHOA	4			
CCND3	4	LEE011	CDK4/6, cyclin D 1/3, p16	NCT0218773

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Trials in Development-MATCH-UP Trial

PI Jonathan Rosenberg, MD



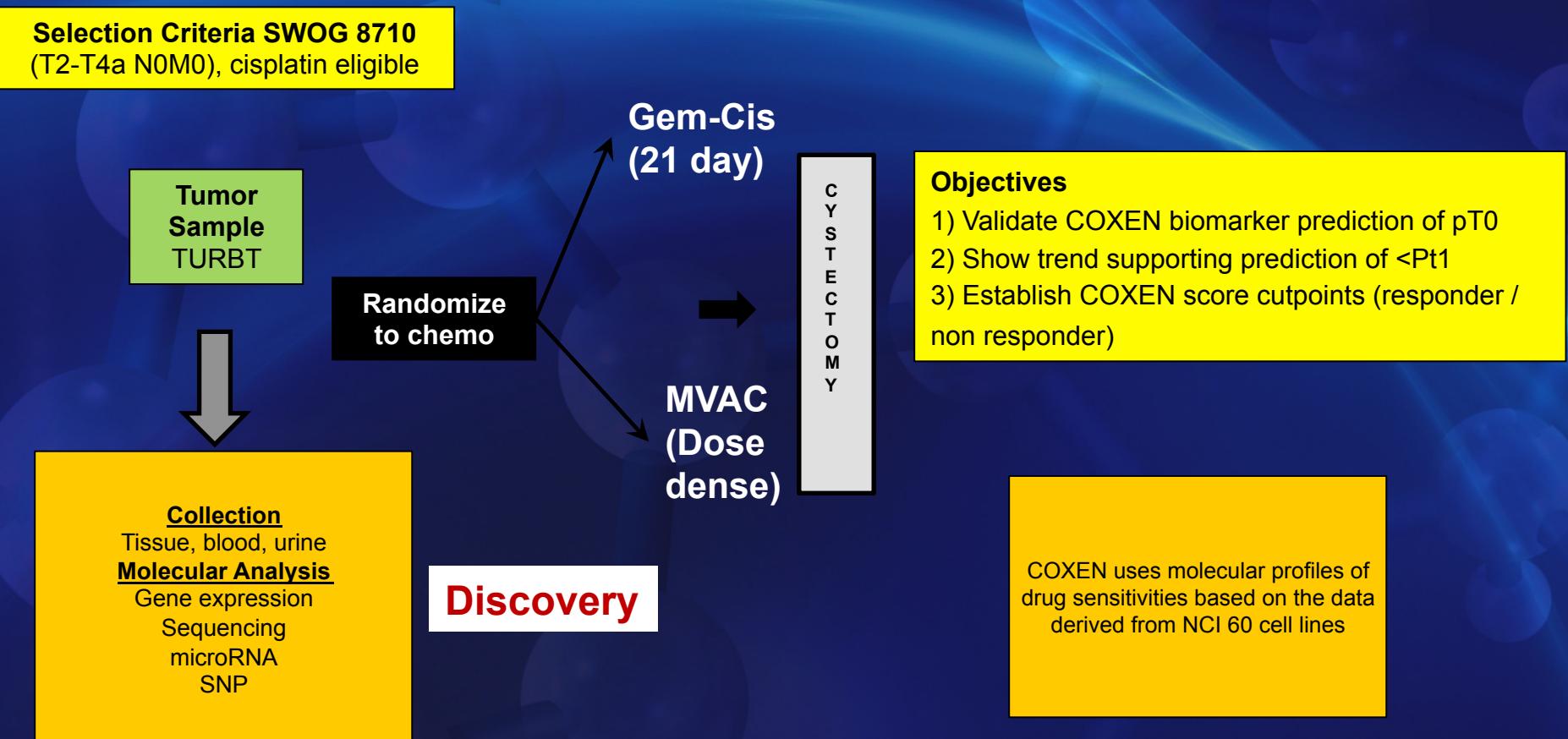
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COXEN - Neoadjuvant Chemotherapy Trial (SWOG)

PI Thomas Flajig MD

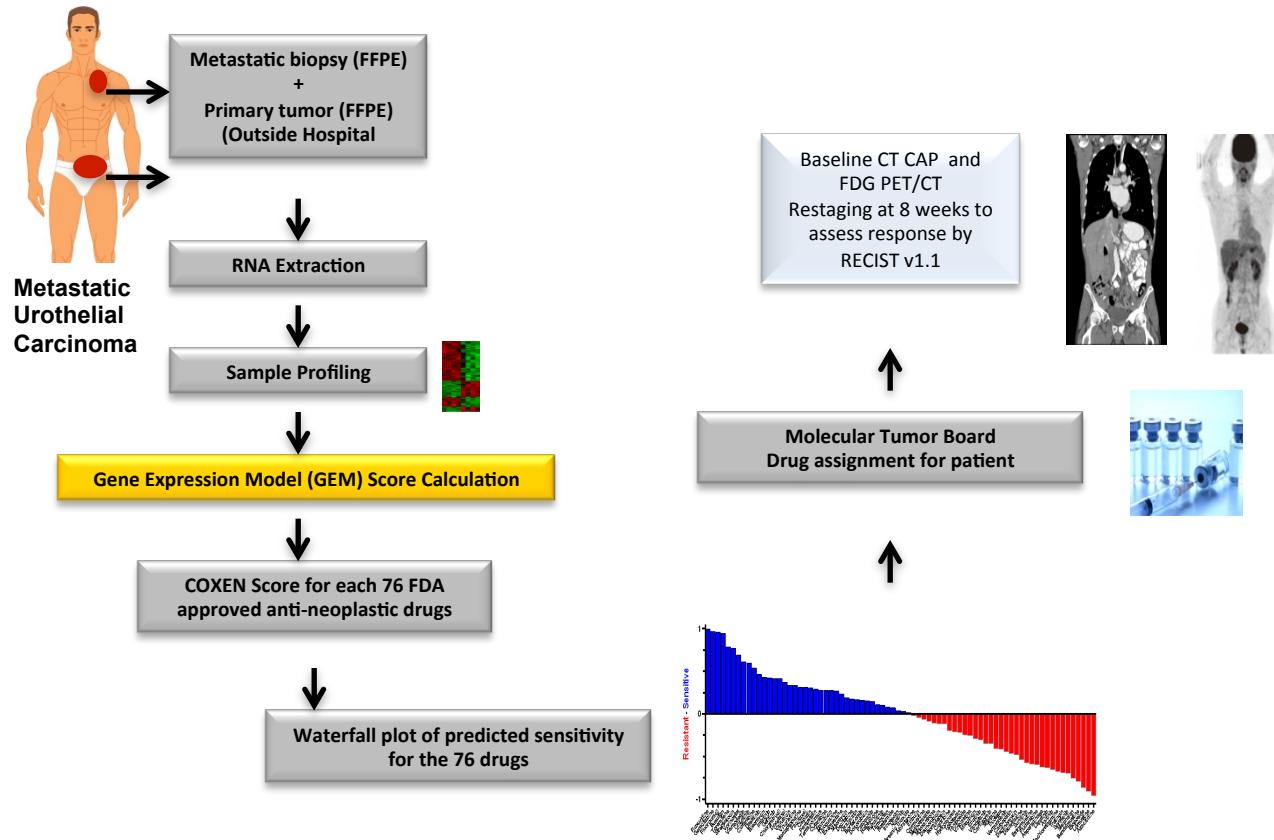
COXEN Biomarker validation and New Biomarker discovery



Presented by: Andrea B. Apolo

National Cancer Institute

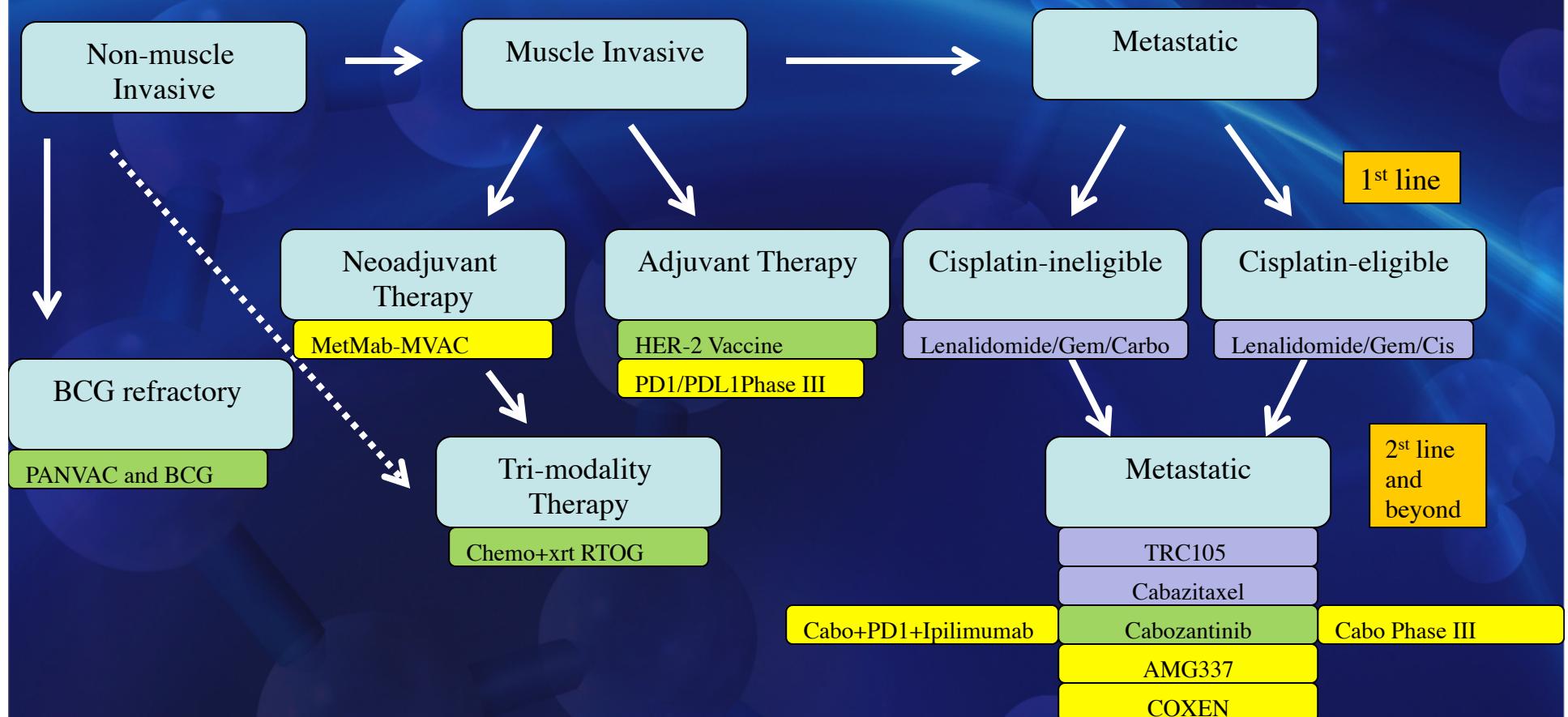
Trials in Development- Genomic Based Assignment of Therapy with COXEN



PI Andrea Apolo, MD

Presented by: Andrea B. Apolo

NCI Bladder Cancer Program



National Cancer Institute

Thank YOU

All my patients and their families

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